"It is possible to believe that all the past is but the beginning of a beginning, and that all that is and has been is but the twilight of the dawn.

It is possible to believe that all the human mind has ever accomplished is but the dream before the awakening."

- H. G. Wells -
“The seat of the soul and the control of voluntary movement - in fact, of nervous functions in general, - are to be sought in the heart. The brain is an organ of minor importance.”

- Aristotle (from “De motu animalium” 4th century B.C.)

Although the Greek philosopher Aristotle regarded the heart, not the brain, as the main organ for intelligence, the brain has intrigued scientists for ages. The first known written reference to the brain is dated to 1700 B.C. and was found on a papyrus roll from ancient Egypt describing the symptoms, diagnosis and prognosis of two patients with head injuries (Kandel et al., 1995). In the 1880s, the Spanish neuroanatomist Santiago Ramón y Cajal described the structure and contacts between cells in the nervous system (Kandel et al., 1995), and it has later been estimated that there are more connections between nerve cells in the brain than there are stars in the universe. These connections can be altered by different events including learning, experience, aging and brain injuries, illustrating the enormous complexity of the brain.

**Cerebral stroke**

Stroke is a major health problem worldwide. In industrialized countries, it is the major cause of long-term disability, and the third leading cause of death after heart disease and all types of cancer (Asplund et al., 1998; Warlow et al., 2003). The understanding of the molecular and biochemical processes during ischemia induced brain damage have increased during recent years, but still there are limited possibilities for treatment of stroke patients. The only approved treatment in clinical practice today, is thrombolytic treatment with tissue plasminogen activator (tPA). Only a relatively small proportion of the stroke patients can benefit from thrombolysis since the treatment has to start within 3 hours of onset of symptoms (Hacke et al., 1995; NINDS, 1995; Brott and Bogousslavsky, 2000). Thus, it is of importance to investigate other potential therapies for stroke patients.

The use of plants for healing purposes predates recorded history and forms the origin of much of modern medicine. Indian and Chinese herbalism are of the most prevalent of the ancient herbal traditions currently practiced. Though synthetic drugs are cheaper to make manufactured on a mass production basis they do not require plants from foreign lands. Nevertheless, certain plant drugs are still extremely important e.g. Glycosides and their derivatives from Digitalis, Curare, from the tropical plant Strychnos toxifera, Morphine, from
Papaver somniferum and Reserpine and its derivatives, from the root of a plant, Rauwolfia serpentina. Curcuma longa L. (family Zingiberaceae) is used extensively Ayurvedic medicine for treatment of inflammatory conditions, skin disease, parasitic infection, jaundice, ulcer etc. (Ammon and Wahl, 1991). The major chemical constituents of turmeric rhizome are volatiles and non-volatiles. The aroma of turmeric is due to its volatile oil (curcuma oil- a group of terpenoids), while the non-volatile compounds, which are found to be a rich source of curcuminoids (curcumin) compounds accounts for its bright yellow color and is now used as a drug for various cancerous diseases.

At present, almost all scientific workers in various fields recognize the importance of plants as sources of biologically active products and have initiated active research programmes either to isolate new lead compounds or to produce standardized extracts. The quest for effective stroke treatments remains an urgent priority. By recognizing the strengths and limitations of animal models of stroke and the shortcomings of previous clinical trials, we hope to move translational research forward for the development of new therapies for the acute and sub-acute stages after stroke. Linking the indigenous knowledge of the medicinal plant to modern research activities to provide a new approach, this makes the rate of discovery of drugs much more effective than with random collection.

Cerebral damage as a consequence of glutamate-mediated excitotoxicity represents a major consequence of stroke. However, the development of effective clinical treatments for this potentially devastating condition has been largely unsuccessful to date, despite promising basic research. The most common causes of ischemic stroke are large artery atherosclerosis, embolisms, thrombosis and small vessel occlusions (Ter Horst and Postigo, 1997; Warlow et al., 2003). Some stroke risk factors are treatable, including high blood pressure, diabetes mellitus, smoking, alcohol abuse, diet, atrial fibrillation, while others are not possible to modify, such as age, gender, race and genetic factors (Ter Horst and Postigo, 1997; Asplund et al., 1998; de Freitas and Bogousslavsky, 2001; Warlow et al., 2003).

**Type of Stroke**

There are two main types of stroke. One is the ischemic stroke and the other is hemorrhagic stroke. Ischemic stroke is the most common type and accounts for about 87 percent of all strokes. It occurs when a blood clot (thrombus) forms and blocks blood flow in an artery due to atherosclerosis. When the blood clot forms within an artery of the brain, it's called a thrombotic stroke. A wandering clot (an embolus) or some other particle that forms
away from the brain, usually in the heart, may also cause an ischemic stroke and is called cerebral embolism. The clot is carried by the bloodstream until it lodges in an artery leading to or in the brain, blocking the flow of blood. It's responsible for 15–20 percent of all strokes. A subarachnoid hemorrhage occurs when a blood vessel on the brain's surface ruptures and bleeds into the space between the brain and the skull (but not into the brain itself). A cerebral hemorrhage occurs when a defective artery in the brain bursts, flooding the surrounding tissue with blood. Hemorrhage (or bleeding) from an artery in the brain can be caused by a head injury or a burst aneurysm.

**Major modes of neuronal death**

To study what causes cell death, cell death has to be recognized. There appear to be at least two distinct modes of cell death that participate in ischemic cell death. There are at least two quite different forms of this cell death, where the cell first shrinks dramatically and becomes very electron dense. Less common is edematous cell change, where the cell swells greatly and organelles lose their form. It is widely termed necrosis or necrotic cell death, but necrosis is really the “decay” process after the point of cell death and occurs in all forms of cell death (Trump and Arstila, 1980). The apoptosis cell death and necrosis or necrotic cell death, is fundamentally different from apoptosis cell death in that it only occurs after an exogenous insult; furthermore, no new structures are elaborated as part of the process. Thus it does not appear to be a programmed. The neurons have the potential for exhibiting all modes of death in response to an ischemic insult. As ATP levels decrease rapidly after severe ischemia, necrotic cell death usually predominates. Although ischemia and ATP depletion typically cause acute cell swelling, ionic imbalances can also trigger cell shrinkage and apoptotic cell death under certain conditions.

**Pathophysiology of ischemic injury**

Normal cerebral blood flow (CBF) in man is typically in the range of 45-50 ml/min/100g between a mean arterial pressure (MAP) of 60 and 130 mmHg. When CBF falls below 20 to 30 ml/min/100g, marked disturbances in brain metabolism begin to occur, such as water and electrolyte shifts and regional areas of the cerebral cortex experience failed perfusion. Ischemic injury focused on relatively simple biochemical and physiological changes: (1) Within 5 minutes, high-energy phosphate levels virtually disappears (ATP depletion) and profound disturbances in cell electrolyte balance start to occur, (2) acidosis due to anaerobic generation of lactate, (3) accumulation of intracellular calcium by oxidation-
dependent calcium sequestration inside the mitochondria along with neutrophil invasion (4) and no reflow due to swelling of astrocytes with compression of brain capillaries. Subsequent research has shown the problem to be far more complex than was previously thought, involving the action and interaction of many factors.

Changes in ionic and energy metabolism

The brain has a very high metabolic rate and requires high levels of oxygen and glucose, but has practically no capacity for energy storage. Interruption of blood flow during acute stroke results in energy depletion since production of ATP is dependent on both oxygen and glucose. Residual glucose is metabolized anaerobically in both astrocytes and neurons, leading to increased lactate production and acidosis. This initiates a cascade of events that is summarized in Fig.1, and has been thoroughly reviewed in (Ter Horst and Postigo, 1997; Dirnagl et al., 1999; Kato and Kogure, 1999; Lee et al., 1999).

Briefly, the energy depletion inhibits the activity of ATP-dependent ion pumps, inducing an influx of extra cellular Na\(^+\) and Cl\(^-\) as well as efflux of K\(^+\) from the cells. This result in passive diffusion of water into the cells, causing edema that affects perfusion of surrounding areas and increases the intracranial pressure. The increased levels of extra cellular K\(^+\) induce depolarization of surrounding cells (spreading depression), which might contribute to the expansion of the lesion. The disturbed ion gradients over the cell membrane cause depolarization of neurons and glial cells. This induces an influx of extra cellular Ca\(^{2+}\) through voltage-gated ion-channels and a release of excitatory amino acids from pre-synaptic terminals, which in combination with a reduced glutamate reuptake results in an accumulation of glutamate and other excitatory amino acids in the extra cellular space.

Activation of NMDA and metabotropic glutamate receptors contributes to intracellular accumulation of the second messenger Ca\(^{2+}\). The resulting intracellular calcium overload stimulates a series of events that lead to tissue damage, including activation of proteases and lipases that promote membrane damage, and activation endonucleases leading to DNA damage. Free radicals also induce the formation of inflammatory mediators that will activate microglia and lead to invasion of inflammatory cells.
Ischemic stroke

- Reduced blood flow
- Energy depletion
- Failure of Na\(^+\)-K\(^+\) pumps
- Acidosis
- Membrane depolarization
- Increased extracellular glutamate levels
- Activation of glutamate receptors (NMDA and AMPA)
- Increased intracellular Ca\(^{2+}\) levels
- Activation of NO synthase, lipases, proteases and endonucleases
- Apoptosis

**Fig.1:** The neurotoxic cascade in the ischemic penumbra.

**Role of Nitric oxide system**

NO is produced by all brain cells including neurons, endothelial cells, and glial cells (astrocytes, oligodendrocytes, and microglia) by Ca\(^{2+}\)/calmodulin-dependent NOS isoforms. Physiologically NOS in neurons (nNOS, type I NOS) and endothelial cells (eNOS, type III NOS) produce nanomolar amounts of NO for short periods in response to transient increases in intracellular Ca\(^{2+}\), which is essential for the control of cerebral blood flow and neurotransmission and is involved in synaptic plasticity, modulation of neuroendocrine functions, memory formation, and behavioral activity (Szabo, 1996; Guix et al., 2005; Moncada and Bolanos, 2006).
It has been demonstrated that NO generation is greatly increased during ischemia (Tominaga et al., 1994; Beasley et al., 1998). However, the alterations in NO and the function of NOS are complex and can either induce injury or exert protection (Dalkara and Moskowitz, 1994). In vitro studies suggest that overproduction of NO results in neuronal toxicity, while in vivo studies suggest that NO has both protective and toxic effects (Nowicki et al., 1991; Dalkara and Moskowitz, 1994).

It is thought that NO derived from nNOS in the ischemic brain is cytotoxic due to its reaction with the superoxide radical with the formation of the potent oxidant peroxynitrite (Fukuyama et al., 1998). However, it is thought that NO generated from eNOS within the vascular endothelium may be protective through inducing vasodilation, which in turn decreases the severity of ischemia. Studies in transgenic mice have demonstrated that knockout out of nNOS results in decreased infarct size in models of focal cerebral ischemia. Conversely, studies in mice with knockout of eNOS have shown exacerbation of injury with increased infarct size. While these studies suggest important opposing roles of NO generation from each isoform, the relative magnitude and time course of NO generation from nNOS and eNOS in the ischemic brain have not been previously determined.

Upon reflow, the O₂ concentration increases sharply and nNOS therefore becomes fully activated. In addition, rapid O₂ availability may exceed the mitochondrial capacity to reduce O₂ to H₂O and hence superoxide anion production may be enhanced. In this case, O₂⁻ (superoxide) avidly reacts with NO to form peroxynitrite (ONOO⁻), which is a well-known irreversible inhibitor of mitochondrial function and a pro-oxidant compound that damages lipids, proteins and DNA, leading to neuronal cell death.

![Diagram](image)  
**Fig.2:** Neurotoxic effect of NO during Hypoxia-Ischemia& Reperfusion
NO and superoxide may damage the cells and tissues with which they interact (Dawson et al., 1993; Dawson and Dawson, 1996). However, peroxynitrite formed from nitric oxide and superoxide (Beckman et al., 1990; Lipton et al., 1993), is considered to be the most damaging of the reactive oxygen species (Beckman et al., 1990; Lipton et al., 1993). ONOO° promotes the nitrosylation of phenolic ring compounds such as tyrosine, resulting in the formation of nitrotyrosine residues.

Because ATP levels decrease rapidly after severe ischaemia, necrotic cell death usually predominates. Although ischemia and ATP depletion typically cause acute cell swelling, ionic imbalances can also trigger cell shrinkage and apoptotic cell death under certain conditions.

**Role of Leukocytes in Focal Ischemic Damage**

The white blood cells contribute to focal ischemic damage after temporary insults (Arvin et al., 1996). Accumulation begins within 6 hrs of the stroke, and there is a striking positive correlation between the amount and duration of leukocyte accumulation (Kochanek and Hallenbeck, 1992).

**Cytokines**

Cerebral ischemia induces expression of various cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-1b and IL-6, in the brain. Following stroke, the cytokine TNF-α is upregulated in injured brain regions of rodents (Liu et al., 1994; Botchkina et al., 1997), and detected at increased levels in blood and cerebrospinal fluid from patients (Sairanen et al., 2001; Zaremba and Losy, 2001). Several experimental approaches to inhibit the effects of TNF-α in acute stroke have reduced the degree of ischemic injury in animal models (Wang et al., 2004). These findings indicate that TNF-α contributes to the progression of brain damage after stroke. However, the actions of TNF-α in stroke are complex, because this cytokine also has been associated with increased neuronal survival (Hallenbeck, 2002). Whether TNF-α influences stroke-induced striatal and hippocampal neurogenesis is not known.

Expression of IL-6 in disease models of epilepsy and cerebral ischemia led to the hypothesis that excitotoxicity and neuronal activity induce this cytokine. Absence of IL-6 has been reported not to affect infarct size or neurological function after cerebral ischemia (Clark et al., 2000), although a recent study performed with more precisely controlled body
temperature yielded different results (Herrmann et al., 2003). The main signal pathway for the action of IL-6 in ischemic brain has never been identified.

**Apoptotic Cell Death**

The overall postulate is that these prolonged ionic and macromolecular changes result from the early events, particularly the increased Ca\(^{2+}\) and free radical production lead to the subsequent major functional changes and in turn triggers cell death, both by apoptosis and necrosis (Ter Horst and Postigo, 1997; Barone and Feuerstein, 1999; Dirnagl et al., 1999; Lee et al., 1999; Hu et al., 2002). Activation of an apoptotic cascade occurs in parallel with the necrotic processes.

Both necrotic and apoptotic cell death mechanisms are activated after cerebral ischemia. However, they are concomitantly active in the same cell or in discrete cell populations is not known. The dominant cell death phenotype is determined by the relative speed of death process. Cells undergoing apoptosis may involve one of several parallel transduction pathways that converge in the expression of a set of death genes.

**Involvement of caspases in apoptosis**

Losses of membrane integrity and organelle failure are the most prominent mechanisms of cell death in ischemia. Both caspase-dependent and caspase-independent mechanisms have been described. Caspases, a family of cysteine aspartases, are constitutively expressed in adult and especially newborn brain cells, particularly neurons (www.nature.com/reviews/neuro). They are cleaved and activated in a sequential manner triggered by stimuli either extrinsic or intrinsic to cells. Mild ischemic injury preferentially induces cell death by an apoptotic-like process rather than by necrosis. Cell type, cell age and brain location render cells more or less resistant to apoptosis or necrosis. Importantly, caspase-dependent cell death utilizes energy in the form of ATP.
A large body of evidence indicates that caspases play a central role in apoptosis. All caspases are synthesized as a single inactive zymogen composed of a variable N terminus prodomain, one large (20 kDa), and one small subunit (10 kDa) joined by a small spacer. The caspase family can be grouped into two classes:

- Initiator (or upstream) caspases (caspase 2, 8, 9, and 10)
- Effector (or downstream) caspases (caspase 3, 4, 5, 6, 7, 11, 12, and 13).

Two major pathways have been identified so far by which initiator procaspases can be activated in response to death-inducing stimuli, resulting in the cleavage of the effector enzymes, which in turn cause cell collapse by cleaving specific substrates. The first pathway is activated by trimerization of death receptors such as TNF-R and Fas by their respective ligands, and recruitment of death effector domain (DED) containing pro-caspases (caspases 8 and 10) into a death inducing signaling complex (DISC). This activation step of caspases 8 and 10 is particularly important because both caspases are capable of activating themselves and other caspases and thereby starting the death signaling (Srinivasula et al., 1996). The second pathway is a death receptor-independent process, and involves mitochondrial changes in the activation of caspase 9. In this mitochondria-dependent pathway, a crucial step is the release of cytochrome c from the mitochondria into the cytosol in response to apoptotic signals (Li et al., 1997).
Mitochondria damage and their role on apoptosis

Three main signals cause the release of apoptogenic mitochondrial mediators proapoptotic members of the Bcl-2 family, elevated levels of intracellular calcium, and reactive oxygen species. Two different major changes have been observed in mitochondria during apoptosis. It has been shown that apoptogenic proteins that normally are sequestered in the mitochondrial inner membrane space, such as cytochrome c and the apoptosis inducing factor (AIF), are released through the outer mitochondrial membrane (Susin et al., 1996; Kluck et al., 1997; Leist et al., 1999; Susin et al., 1999).

Cytochrome c is an essential redox component of the respiratory electron transfer system. It is located in the mitochondrial intermembrane space, non-covalently attached to the inner membrane, and contributes to the formation of the mitochondrial transmembrane potential and to oxidative phosphorylation. Cytochrome c may be shuttled to the cytosol via specific pores or transporters, thereby increasing the permeability of the outer mitochondrial membrane. Alternatively, physical rupture of the outer mitochondrial membrane might result in an overall loss of outer membrane integrity and of intermembrane constituents.

Once cytochrome c is released into the cytosol, the cell is committed to die by either a rapid apoptotic mechanism involving the apoptosome-mediated caspase 9 activation (Lee and Shacter, 1997) or by a slower necrotic process probably due to mitochondrial failure. It has also been shown that active caspases can disrupt mitochondrial barrier function (Marzo et al., 1998). The report about an initial, caspase-independent cytochrome c release followed by a caspase-mediated drastic loss of mitochondrial cytochrome c may proof the existence of such amplifying feedback loops at least in some models (Chen et al., 2000).

Bcl-2/Bax System

Anti-apoptotic proteins, such as Bcl-2 and Bcl-xL, were found to be located in mitochondrial membranes (Hockenbery et al., 1990), ii) pro-apoptotic proteins, such as Bax, target the mitochondrial membrane and can induce cell death even when caspase are inactivated (Crompton, 2000), iii).Cells lacking these two proteins fail to undergo apoptosis in response to a wide range of apoptotic stimuli (Wei et al., 2001). Thus, the relative balance between the levels of antiapoptotic and proapoptotic Bcl-2 proteins may be an important determinant of whether a cell lives or dies. Thus, mitochondria were increasingly implicated as sensors and executioners in the cell’s decision about life and death (Kroemer et al., 1997; Reed, 1997; Murphy et al., 1999).
**Review of Literature**

Fig.4: Mitochondria sense the presence of high-concentrations of NO by releasing pro-apoptotic components of the mitochondrial intermembrane space, among them cytochrome c and apoptosis inducing factor (AIF). This release of mediators can result both from the increase or decrease of the mitochondrial inner membrane potential. NO might promote the nitrosylation and/or nitration of these mediators. However, the effects of these post-translational modifications on downstream steps of the apoptotic pathway remain to be better characterized.

**Role of p53**

The tumor suppressor p53 is a transcription factor that promotes cell cycle arrest or apoptosis in response to genotoxic stress by activating or repressing an array of target genes (Levine, 1997). Several studies have shown that p53 plays an important role in neuronal death induced by insults that cause acute neuronal injury or toxicity (Morrison et al., 2003). Mice lacking p53 are significantly protected against neuronal death induced by ischemia (Trimmer et al., 1996). p53 expression is elevated in many paradigms of neuronal injury and overexpression of p53 in normal cultures of sympathetic and cerebellar granule neurons promotes apoptosis (Jordan et al., 1997). While p53 plays an essential role in several models of neuronal apoptosis, death of neurons induced by trophic factor withdrawal (Herzog et al., 1998). The mechanism by which p53 promotes neuronal death is not fully understood. It is known that p53 activates the transcription of many genes that regulate the intrinsic cell death pathway.
Ischemic Infarct

Focal ischemia produces a contiguous mass of damaged brain tissue termed the infarct. In focal ischemia in the core of the lesion, the blood flow is almost always higher so that longer insults are required to get damage. There is a significant gradation of ischemia from the core of the lesion to its outermost boundary, and hence there are different metabolic conditions within the affected site. This heterogeneity, makes the insult much more complex.

The final size of the brain infarct is affected by the penumbra, a region surrounding the core of the infarct where blood flow is below the metabolic demand but energy levels allows to keep neurons structurally intact (Dirnagl et al., 1999; Kato and Kogure, 1999; Heiss, 2000). Cells in the infarct core are generally considered to be beyond rescue. The cells in the penumbra region can potentially be rescued, making it an interesting therapeutic target. The final stage of infarct development in focal ischemia is pan-necrosis, in which the neuronal death is accompanied by glial and vascular cell death and loss of cellular elements. The basis for pan-necrosis is not clear, but for some reason, both the endothelial and glial cells become major targets (Bhat et al., 1996).

Neurogenesis

Following a century of doubt and controversies, there is now a consensus that neurogenesis occurs in the adult brain in at least two regions, the SVZ and the DG. Adult neurogenesis is broadly defined as the birth and maturation of new neurons that add to, or replace neurons in, existing circuitry under normal physiological or pathological conditions. Neurogenesis comprises at least five processes, which partially overlap: viz. proliferation of stem cells and progenitors, migration of newborn cells, neuronal differentiation, integration into neuronal circuits, and survival of cells.

With the recent observations that acute insults to adult brain stimulate new neuronal formation in various species of animals, optimism is building for a possible regeneration of stroke-damaged brain. There are numerous proposed regenerative approaches to neurological diseases. These include cell therapy approaches in which cells are delivered intracerebrally or are infused by an intravenous or intra-arterial route; stem cell mobilization approaches.

Neural stem/progenitor cells

A neural stem cell is defined as a cell that: 1, can generate neural tissue or is derived from the nervous system; 2, has capacity for long-term self-renewal, and; 3, displays
multipotency, i.e. the capacity to generate differentiated progeny of the neuronal, astroglial and oligodendroglial lineages, as well as multipotent stem cells (Gage, 2000).

Cerebral ischemia stimulates the proliferation of progenitor cells in rodents and humans (Zhang et al., 2004a; Jin et al., 2006). New neurons migrate to the ischemic striatum (Arvidsson et al., 2002; Parent et al., 2002) and cortex (Jin et al., 2003); many of the newborn cells die, but some survive and are integrated in neuronal circuits (Nakatomi et al., 2002). This suggests that neurogenesis contributes to functional recovery after stroke, although direct evidence for the functional significance of neurogenesis is lacking.

Neurogenesis in the adult brain is the production of new neurons in several areas of the brain, including the sub-ventricular zone (SVZ) and sub-granular zone (SGZ) of the hippocampus (Gage, 2002). New cells migrate from the SVZ to the olfactory bulb via the rostral migratory stream and differentiate into neurons and glia (Luskin, 1998; Craig et al., 1999; Alvarez-Buylla et al., 2002). Cells from the sub-granular zone migrate a short distance to the granular cell layer of the dentate gyrus (Cameron and McKay, 2001; Alvarez-Buylla and Garcia-Verdugo, 2002; Song et al., 2002) Some newly formed neurons integrate functionally into the neuronal circuitry (Magavi et al., 2000; van Praag et al., 2002). Glial cells produced within the germinal zones may also participate in injury response and repair.

This formation of new neurons plays a number of physiological roles including the replacement of damaged neurons (Nakatomi et al., 2002; Kokaia and Lindvall, 2003), memory formation (Shors et al., 2001; Kempermann and Gage, 2002) response to stress (Mirescu et al., 2004) and in depression (Nakagawa et al., 2002; Santarelli et al., 2003).

**Neurogenesis and Functional Recovery**

Adult neurogenesis in the brain is related to the recovery of neurological function. Inhibition of neurogenesis in the dentate gyrus of adult mice by blocking VEGFR2 significantly impairs learning capability in the mice, as assayed by water-maze measurements (Cao et al., 2004). Liu and her colleagues (Liu et al., 1998) demonstrated by using ionizing radiation to decrease neural regeneration after global ischemia in the rat that reduction of neurogenesis reduces functional recovery measured by the water-maze (Raber et al., 2004). Whether neurogenesis improves functional recovery after stroke is uncertain; however, a body of literature supports the hypothesis that increased neurogenesis should result in functional improvement (Kondziolka et al., 2000; Stilley et al., 2004; Zhang et al., 2005). Consistent with these data, are data in patients with basal ganglia stroke, showing that
transplantation of neuronal cells enhances cognitive function six months after transplantation (Stilley et al., 2004).

Neural stem cells undergo symmetric or asymmetric cell divisions. In a symmetric division, both progeny will be stem cells. In contrast, an asymmetric division produces one new stem cell that is identical to the mother cell and one cell that is more determined for a certain lineage of differentiation. These daughter cells have less stem cell properties and are termed progenitor cells.

The production of new neurons, neurogenesis, occurs in the adult mammalian central nervous system (CNS) following the migration and differentiation of neural stem/progenitor cells (NSPCs). The majority of these cells reside in one of two germinal zones; the subventricular zone in the wall of the lateral ventricles (SVZ) and the subgranular zone of the hippocampus (SGZ) (Taupin and Gage, 2002). Outside of these regions, cell proliferation is common but the result is primarily the production of glial cells (Palmer et al., 1999).

Fig.5: Schematic picture of how quiescent neural stem cells undergo self-renewal as well as give rise to more restricted neural progenitors. These neural progenitors display limited capacity for self-renewal and may differentiate into mature neurons, astrocytes and oligodendrocytes.
Neuronal stem cells (neural progenitor cells, NPCs) can give rise to astrocytes, neurons and oligodendrocytes. In adult rodents, experimental stroke triggers neurogenesis in the brains. The induction is robust and has been observed in global and focal models and in several species. Both forms of ischemia have been reported to stimulate neurogenesis in the sub-ventricular zone and in the sub-granular zone of the hippocampus.

In a recent study of unilateral middle cerebral artery (MCA) occlusion in the rat, BrdU-labeled cells from the SVZ that co-expressed DCX, and later NeuN, migrated into the ischemic striatum, but not the ischemic cerebral cortex (Arvidsson et al., 2002). In another study, transient forebrain ischemia in rats was followed by replacement of hippocampal CA1 pyramidal neurons with BrdU- and NeuN-immunopositive cells that appeared to arise from nearby periventricular precursors (Nakatomi et al., 2002).

**Angiogenesis**

After ischemic stroke, there is neovascularization around the infarcted area, which is called penumbra. Angiogenesis and arteriogenesis are responsible for the new vessel formation. Until recently, vasculogenesis has been proved to involve mechanisms in postischemic neovascularization, which was thought to be restricted to embryonic development. New blood vessels' formation is a complex pathologic process after ischemic stroke, in which many factors are properly involved. Functional recovery was found after stroke, which may contribute to angiogenesis in the periinfarct tissue. Thus, therapeutic angiogenesis has been initially studied in animal models, but there is still a long way to go for therapeutic angiogenesis to be used in the treatment of stroke patient. Angiogenesis and neurogenesis are coupled in the brain. Increasing angiogenesis with adult stem cell approaches in rodent models of stroke leads to preservation of neurones and improved functional outcome. Neurogenesis and angiogenesis may open unique therapeutic approaches and drug intervention for the preservation of cells in stroke and neurodegenerative disorders.